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The Pathology of Tay-Sachs' Disease

*Abstracts of Papers**

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During the latter part of the past century Sachs isolated a number of cases from the broad category of infantile mental deficiency, designating them as instances of arrested cerebral development. With his further contact with the disease, salient features emerged which furnished greater individuality to this entity. A familial tendency became apparent; the rapidly developing blindness seen in Sachs' first case was a constantly repetitive observation. Sachs incorporated these defining elements and applied the more appropriate term, amaurotic family idiocy, to the disease.

In the years that have followed newer concepts of the disease have evolved. Descriptions of cases in the late infantile, juvenile and even adult period of life have revealed that the disease cannot be consigned to its original narrow age limit. The seven cases embodied in the present report, however, all fall in the infantile category. The presenting symptoms, with some variation, were quite similar. Arrest and regression of development, apathy, weakness and amaurosis were apparent. Hyperacusis was an outstanding feature in the majority of the cases.

At autopsy only a paucity of alterations was grossly apparent, none bearing any distinctive quality. In some instances the pattern of surface fissuration was overly simplified and the sulci unduly broadened. Gross sectioning of the central nervous system rarely brought to light any additional abnormality. In striking contrast to the meager and non-specific results of gross visualization, microscopic examination disclosed cellular alterations of such universal distribution that no slide of the nervous system failed to exhibit the histopathology distinctive of the disease. The primary cellular alterations resided exclusively in the neurons. All other changes in glial and mesodermal elements were considered as responsive to ganglionic degradation. Neuronal involvement was exclusive and ubiquitous; neurons of the entire autonomic system shared equally in the process. The cytologic sine qua non of Tay-Sachs' disease is an enlarged neuron which has lost its angular configuration. The Nissl substance is diminished in amount, the residuum compressed about an eccentric nucleus. The

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incremented cytoplasmic volume results from the presence of pale-staining, hematoxylinophilic, refringent granules. This abnormal prelipoid substance is minimally sudanophilic. Neurofibrils are displaced peripherally but appear unaffected by the compression till the cell itself degenerates. While no neuron is spared in the extensive changes inherent to the dystrophic process, some topographic variation is often demonstrable. The neurons of the cerebellar and retinal molecular layers are less implicated than other neurons of the nervous system. Actual loss of neurons is not conspicuous except in the cerebral cortex where neurocellular depletion is at times prominent.

In one case in which there occurred convulsive seizures of a myoclonic variety, cytoplasmic inclusion bodies were seen in the basal ganglia and thalamus. These bodies were eosinophilic and possessed the tinctorial capacities of inclusion bodies often associated with clinical states of myoclonus epilepsy. It would appear that these structures are nosologically unrelated to Tay-Sachs' disease but represent a phase of degeneration common to many neurologic states.

Demyelination of an inconspicuous and patchy nature was seen in the cerebral white matter. This feature has been described only in the infantile variety of the disease. Assuming that the later forms of amaurotic family idiocy are delayed instances of the same disease process, it can be hypothesized that arrest of myelin formation rather than destruction of existing myelin is the mechanism operative in the infantile variety of the disease. Myelination is not normally complete at birth but proceeds through a neonatal period coincident with the appearance of the neurologic symptoms of Tay-Sachs' disease. In such zones of myelin depletion no evidence of recent breakdown can be demonstrated, a finding that offers further support to the concept that inhibited development of myelin is a feature of the dystrophic disease.

Microglial cells react to the slow process of neuronal dissolution. Large numbers of activated microglia filled with intensely sudanophilic material congregate in areas of gray matter. The difference in staining qualities between the neuronal prelipoid and the phagocytosed neutral lipid indicates that some chemical breakdown occurs following liberation of the substance distending ganglionic cytoplasm. A mild astrocytosis is also seen.

The rounded microglia migrate toward neighboring perivascular areas, crowding these spaces with lipid-filled cells. Ultimately, endothelial cells participate in the scavenger activity and become distended with demonstrable lipid. In two cases of Tay-Sachs' disease in which autopsies were performed, these altered endothelial cells formed niduses for fibrin deposition eventuating in thrombotic occlusion. Grossly there were multiple small zones of cerebral encephalomalacia. The marantic state of these infants undoubtedly also contributed to this process of thrombosis of cerebral veins. Other microglial phagocytes within the perivascular spaces migrate to the subarachnoid space, evoking there a cellular proliferation. Grossly this is expressed as thickening and opacity of the meninges.

In many cases a history is obtained indicating an abrupt onset of the illness. The child is usually described as normal up to a certain point at which time developmental progress is aborted and the characteristic features of the disease emerge. It would appear that a saturation point is reached beyond which neural maturation cannot proceed. One of the patients in the present report was submitted to a routine physical examination at the age of seven months. This apparently healthy infant showed no abnormal findings except for evidence of early bilateral macular degeneration. Three months later the first neurologic signs of Tay-Sachs' disease were elicited. The circumstances in this case would indicate that neurons affected by the dystrophic process relinquish their basic functions only with reluctance and that a remarkable integrity of such functions is maintained until relatively late in the course of this particular degenerative process.

Sections of retina disclose a process analogous to the changes seen elsewhere in the nervous system. The ganglionic cells are conspicuously swollen and contain prelipoid cytoplasmic inclusions.

The cell alterations so intimately associated with amaurotic family idiocy lose their aura of specificity since similar or identical cells have been occasionally observed in gargoylism, Gaucher's disease, congenital spastic paralysis, syndromes akin to Friedreich's ataxia and Niemann-Pick's disease. Since morphologic interpretation may at times be invalid and represent a common visual denominator of many varieties of ganglionic degeneration, the postulated identity of Tay-Sachs' disease and Niemann-Pick's disease is open to question. The adventitious substance deposited in neurons in Tay-Sachs' disease differs in chemical structure from that recovered in instances of Niemann-Pick's disease with nervous system involvement. In two cases of Niemann-Pick's disease included in the present series there were significant elevations of serum lipid and phospholipid, a change not seen in Tay-Sachs' disease.

Conclusions

One can conceive of this disease as a focal enzymatic anomaly of genetic background, the morphologic and clinical expression of which is restricted to one portion of the neuro-ectoderm. Further, that this anomaly is basically not concerned with the essential vegetative functions of the cell, but rather a selective aspect of lipid metabolism. Investigations in the field of embryology have shown that in the earlier phases of normal embryonic development, only proteins are found in neurons. At a later stage, the lipid constituents can be demonstrated. Sobotka feels that the basic defect lies in an abnormality of the esterases concerned with transesterification. Therefore, not until such time as the cerebrosides normally enter the ganglion cell could there be any endogenous production of aberrant intermediary substances. And until such time, it would appear that the normal cell can evolve normally.

The progressive accumulation of this metabolic variant within the ganglion cell apparently produces the degenerative alterations. Since development proceeds until such time as the accumulated prelipoids express their morbid effects, this can be considered an indication that the enzymatic abnormality is not fundamentally concerned with basic neuronal function.

The human brain is not fully developed at birth and maturation proceeds through the neonatal period. A critical point in this disease is reached when further development is aborted and regression ensues. In this sense, Sachs' initial concept of arrested development validly describes the disease bearing his name.

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*Diffuse Sclerosis in an Infant: Metachromatic Leukoencephalopathy**

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A case of diffuse sclerosis with the deposition of metachromatic material (metachromatic leukoencephalopathy) was presented. The disease occurred in a male infant dying six weeks after a six week premature birth. The mother was diabetic, and her disease was poorly controlled during pregnancy. The clinical course was characterized by episodes of apnea, bradycardia, and rigidity, followed by tonic and clonic convulsive seizures. No specific neurologic abnormalities were observed between such episodes. There were no other significant abnormalities.

At autopsy a severe degenerative process

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